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14. ABSTRACT

A small, lightweight microdevice has been developed for activity-dependent stimulation (ADS) and successfully tested for functionality in both anesthetized and ambulatory rats. Further, in semi-chronic experiments in rats with TBI using this microsystem, an unprecedented, potent effect of ADS on motor performance has been demonstrated, as compared to control rats (injured but no microdevice) and open-loop stimulation (OLS) rats. Specifically, open-loop stimulation does result in some recovery after injury, but ADS is significantly more efficacious, resulting in recovery to normal ranges of performance within 2 weeks after injury.

15. SUBJECT TERMS
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A Brain-Machine-Brain Interface for Rewiring of Cortical Circuitry after Traumatic Brain Injury

Award Number W81XWH-10-1-0742
Randolph J. Nudo, PhD
Annual Report
November 2012

INTRODUCTION:

The goal of this project is to use an implantable brain-machine-brain interface to enhance behavioral recovery after traumatic brain injury by reshaping long-range intracortical connectivity patterns. We hypothesize that artificial synchronous activation of distant cortical locations will encourage spontaneously sprouting axons to migrate toward and terminate in the coupled region, and that such directed sprouting can aid in functional recovery.

BODY:

Substantial progress has been made in demonstrating proof-of-concept for our approach in a rodent model of traumatic brain injury. The Tasks at Kansas University Medical Center comprise the neurobiology components of the collaborative project with investigators at Case Western Reserve University who are performing the electronics and microsystem packaging components. We have now confirmed our preliminary findings of rapid recovery of motor abilities in rats implanted with the microdevice. In Project Year 2, we completed the groups of control rats (injured but no microdevice) and implanted rats. In addition, as noted in our Year 2 plans in the first progress report, we completed a group of "open-loop control" rats. This critical control demonstrated that open-loop stimulation results in some recovery after injury, as expected, but that activity-dependent stimulation is significantly more efficacious, resulting in recovery to normal ranges of performance by 14 days post-injury. These results have been compiled in manuscript form and submitted to the journal, *Nature.* The manuscript received very favorable reviews, but several additional sets of analyses are required before resubmission. We are currently gathering the additional material, and will resubmit the revised manuscript within several weeks.

In the text that follows, we first summarize the results of our in-vivo proof-of-concept study, and then address progress toward each of the Year 2 tasks.

Manuscript submitted to Nature: Restoration of function after brain damage using a neural prosthesis (Complete main body of manuscript is included in the appendix.)

Authors: David J. Guggenmos, Meysam Azin, Scott Barbay, Jonathan D. Mahnken, Pedram Mohseni, Randolph J. Nudo

Summary: Neural interface systems are becoming increasingly feasible for brain repair strategies. This paper tests the hypothesis that recovery after brain injury can be facilitated by a neural prosthesis serving as a communication link between distant locations in the cerebral cortex. The primary motor area in the cerebral cortex was injured in a rat model of focal brain injury, disrupting communication between motor and somatosensory areas and resulting in impaired reaching and grasping abilities. After implantation of microelectrodes in cerebral cortex, a neural prosthesis discriminated action potentials (spikes) in premotor cortex that triggered electrical stimulation in somatosensory cortex continuously over the subsequent weeks. Within one week, while receiving spike-triggered stimulation, rats showed substantially improved reaching and grasping functions that were indistinguishable from pre-lesion levels by two weeks. This proof-of-concept study demonstrates that neural interface systems can be used effectively to functionally bridge damaged neural pathways and promote recovery after brain injury.

Progress towards Phase II (year 2) tasks

Task 1. Induce TBI in rats to destroy CFA (and leave RFA intact) using the controlled cortical impact (CCI) device.

We have demonstrated that we can make reliable focal injuries to CFA that result in prolonged behavioral deficits in rats. We have also demonstrated that the injuries spare the RFA, the intended location for recording electrodes. This task has been completed. A paper describing these results was published during year 1 (Nishibe et al., 2010).

Task 2. Conduct baseline testing of forelimb use in injured rats in reach/retrieval task and foot-fault test.

We now have extensive data on these two tasks in injured rats. Results are described in a published paper (Nishibe et al., 2010).

Task 3. Randomize rats to one of four groups (n = 6) each counterbalanced with respect to baseline forelimb motor performance.

We have completed Task 3, though details of the randomized groups has been amended for two reasons: First, our preliminary anatomical studies in normal rats suggests that the connections between the target premotor area and parietal cortical areas are not as discrete as once thought. Instead, they are more diffuse, and only differ quantitatively. Thus, randomizing the groups based on connectivity patterns was not feasible. Second, because our preliminary data demonstrating rapid recovery in rats with microdevices was so compelling, it was necessary to employ an important control group to determine if recovery was due to stimulation alone. In this group, microdevices were implanted, but stimulation was not contingent on neural activity in the recorded area. We refer to this group as the "open-loop stimulation" group in the attached manuscript. Thus, the experiment contained three groups with 6 rats each: activity-dependent stimulation, open-loop stimulation and control. The fourth group of rats (n=6) was part of a separate study to further determine whether physiological changes occur in the spared motor area as a result of the stimulation.

Task 4. Staging 4 rats at a time (one per group), implant the microsystem and place the recording microelectrode at the center of the RFA.

Due to time requirements for maintenance of the rats, we have found that only 2 rats can be staged at a time. Thus, while the studies required more time, we completed this task within the original time frame.

Task 5. Place the stimulating electrode in S1 hand area, S2, or barrel field. Two of the 3 areas will be examined.

Because of the more diffuse pattern of connectivity between the premotor area and these intended regions, and because of the unexpectedly rapid recovery observed with S1 stimulation, we decided to focus solely on this area.

Task 6. Prepare a control group of implanted and brain-injured rats (n = 6) with uncorrelated stimulation of somatosensory areas.

This control group has been completed as described above.

Task 7. Conduct stimulation protocol during active phase for 12 hours/day, 5 days per week, for one month.

This task has been completed for the three groups (activity-dependent stimulation, open-loop control, unimplanted control). Since the microdevice battery lasted for more than 24 hours, we were able to extend the protocol stimulation to 24 hours.

Task 8. Assess physiological and behavioral endpoints once per week.

This task has been completed for the behavioral endpoints in the three groups of rats. Physiological endpoints are currently being examined and will be submitted with the revised manuscript.

Task 9. Explant microsystem and inject an anatomical tract tracer into the RFA at PD 30.

This task has been completed for the three groups of rats.

Task 10. Euthanize animals 1 week post injection & remove brain/spinal cord for histological studies in Phase III.

This task has been completed for the three groups of rats.

Task 11. Analyze evoked LFPs and spike discharges in ambulatory animal experiments to determine temporal profile of physiological endpoints.

We are currently focusing on spike discharges, and analyzing the temporal profile of physiological endpoints with respect to phase of movement.

KEY RESEARCH ACCOMPLISHMENTS:

- Completed all regulatory requirements to continue study
- Demonstrated rapid recovery of motor performance in rats undergoing activity-dependent stimulation
- Completed controlled study of activity-dependent stimulation compared with open-loop stimulation and unimplanted controls
- Submitted manuscript for publication

REPORTABLE OUTCOMES (YEAR 2 only):

1- Manuscripts/Abstracts/Presentations:

Peer-reviewed journal publications:

- Guggenmos, D.J., M. Azin, S. Barbay, J.D. Mahnken, P. Mohseni and **R.J. Nudo**. Restoration of function after brain damage using a neural prosthesis. Under review.

Abstracts:

- Azin, M, Guggenmos, D, Barbay, S, **Nudo, RJ** and Mohseni, P (2012) Activity-dependent intracrotical microstimulation for driving functional behavioral recovery in the rat after traumatic brain injury. Neural Interfaces Conference 2012, Salt Lake City, Utah.
- Guggenmos, DJ, Azin, M, Barbay, S, Mohseni, P, and **Nudo, RJ** (2012) Driving functional behavioral recovery in the rat using activity-dependent stimulation. Program No. 682.16. 2012 Neuroscience Meeting Planner. New Orleans, LA. Society for Neuroscience, 2012. Online.
- Nishibe M, Barbay S, and **Nudo, R J** (2012) Different neurophysiological and behavioral consequences of traumatic brain injury (TBI) versus ischemic infarct in the rat. Program No. 680.11. 2012 Neuroscience Meeting Planner. New Orleans, LA. Society for Neuroscience, 2012. Online.

Oral presentations (Dr. Nudo):

- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, American Society for Neurorehabilitation Clinician Scientist Award lecture, ASNR-ACRM Joint Educational Conference, Atlanta, Georgia, October 14, 2011.
- Invited Speaker, *Repairing the Brain after Injury*, Annual War and Recovery Day, Brain Injury Association of Kansas and Greater Kansas City, November 4, 2011.

- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, Neurobiology of Disease Course, University of Texas Health Science Center, Houston, Texas, November 30, 2011.
- Invited Speaker, N*ew tools for building artificial communication bridges in the injured brain*, Neurobiology and Anatomy Seminar Series, University of Texas Health Science Center, Houston, Texas, December 1, 2011.
- Invited Speaker, *Current Research in Brain Injury Recovery,* Brain Injury Association Professional Conference, Brain Injury Association of Kansas and Greater Kansas City, Overland Park, Kansas, March 29, 2012.
- Invited Speaker, *Advances in smart prosthetics for modulating neural pathways after brain injury*, 7th International Symposium on Neuroprotection and Neurorepair, Potsdam, Germany, May 3, 2012.
- Keynote Speaker, *Translational Research Processes,* Satellite Symposium entitled "Establishing Collaborations and Priorities in Clinical and Translational Stroke Rehabilitation Research", Hunter Medical Research Institute, Hunter, Australia, May 14, 2012.
- Keynote Speaker, Michael Barnes Lecture, *Harnessing the potential of neuroplasticity to improve recovery after brain injury,* 7th World Congress of NeuroRehabilitation, Melbourne, Australia, May 17, 2012.
- Invited Speaker, *Novel neuroprosthetic tools for repair of the injured brain*, International Neuropsychological Symposium, Bonifacio, Corsica, France, June, 2012.

2- Patents and Licenses Applied for/Issued:

- Randolph J. Nudo, P. Mohseni, D. Guggenmos, and M. Azin, *Methods and Associated Neural Prosthetic Devices for Bridging Brain Areas to Improve Function*, International Application No. PCT/US2012/42381 Filed on June 14, 2012
- Randolph J. Nudo, P. Mohseni, D. Guggenmos, and M. Azin, *Methods and Associated Neural Prosthetic Devices for Bridging Brain Areas to Improve Function*, U.S. Application No. 13/523,597 Filed on June 14, 2012
- Randolph J. Nudo, P. Mohseni, D. Guggenmos, and M. Azin, *Methods for Bridging Brain Areas and Associated Neural Prosthetic Devices,* U.S. Provisional Application No. 61/543,593 Filed on October 5, 2011

3- Degrees Obtained from Award:

- David Guggenmos, PhD, Department of Molecular and Integrative Physiology (RJ Nudo, mentor), awarded June 2012

4- Development of Cell Lines and Tissue/Serum Repositories: Not applicable.

5- Infomatics (Databases and Animal Models): None yet.

6- Funding Applied for: None yet.

7- Employment/Research Opportunities Applied for/Received: None yet.

CONCLUSION:

Rapid progress is being made toward developing smart prosthetic platforms for altering plasticity in the injured brain, leading to future therapeutic interventions for TBI that are guided by the underlying mechanisms for long-range functional and structural plasticity in the cerebral cortex. An unprecedented, potent effect of activity-dependent stimulation (ADS) on motor performance has been demonstrated in rats with TBI. Statistical

analysis of the data is complete, and includes both unimplanted control and open-loop stimulation control groups.

REFERENCES:

- Nishibe, M., S. Barbay, D. Guggenmos and **R.J. Nudo** (2010) Reorganization of motor cortex after controlled cortical impact in rats and implications for functional recovery. J Neurotrauma, 27:1-12. (prior publication referenced in annual report)

APPENDIX:

- Guggenmos, D.J., M. Azin, S. Barbay, J.D. Mahnken, P. Mohseni and **R.J. Nudo**. Restoration of function after brain damage using a neural prosthesis. Under review.

APPENDIX

Main body of manuscript submitted to Nature:

Restoration of function after brain damage using a neural prosthesis

Authors: David J. Guggenmos, Meysam Azin, Scott Barbay, Jonathan D. Mahnken, Pedram Mohseni, Randolph J. Nudo

Summary

Neural interface systems are becoming increasingly feasible for brain repair strategies. This paper tests the hypothesis that recovery after brain injury can be facilitated by a neural prosthesis serving as a communication link between distant locations in the cerebral cortex. The primary motor area in the cerebral cortex was injured in a rat model of focal brain injury, disrupting communication between motor and somatosensory areas and resulting in impaired reaching and grasping abilities. After implantation of microelectrodes in cerebral cortex, a neural prosthesis discriminated action potentials (spikes) in premotor cortex that triggered electrical stimulation in somatosensory cortex continuously over the subsequent weeks. Within one week, while receiving spike-triggered stimulation, rats showed substantially improved reaching and grasping functions that were indistinguishable from pre-lesion levels by two weeks. This proof-of-concept study demonstrates that neural interface systems can be used effectively to functionally bridge damaged neural pathways and promote recovery after brain injury.

Introduction

The view of the brain as a collection of independent anatomical modules, each with discrete functions, is currently undergoing radical change. New evidence from neurophysiological and neuroanatomical experiments in animals, as well as neuroimaging studies in humans, now suggests that normal brain function can be best appreciated in the context of the complex arrangements of functional and structural interconnections among brain areas. While mechanistic details are still under refinement, synchronous discharge of neurons in widespread areas of the cerebral cortex appears to be an emergent property of neuronal networks that functionally couples remote locations[1]. It is now recognized that not only are discrete regions of the brain damaged in injury or disease, but perhaps more importantly, the interconnections among uninjured areas are disrupted, potentially leading to many of the functional impairments that persist after brain injury[2]. Likewise, plasticity of brain interconnections may partially underlie recovery of function after injury[3].

Technological efforts to restore brain function after injury have focused primarily on modulating the excitability of focal regions in uninjured parts of the brain[4]. Purportedly, increasing the excitability of cortical circuitry that is involved in adaptive plasticity processes expands the neural substrate potentially involved in functional recovery. However, no methods are yet available to directly alter the functional connectivity between uninjured brain regions, with the intent to restore normal communication patterns. The present paper tests the hypothesis that an artificial communication link between uninjured regions of the cerebral cortex can restore function in a rodent model of traumatic brain injury (TBI). Development of such neuroprosthetic approaches to brain repair may have important implications for the millions of individuals who are left with permanent motor and cognitive impairments after acquired brain injury, as occurs in stroke and trauma.

A brain-machine-brain interface for neural repair

For the present experiment, we utilized a rodent model of focal brain injury to the caudal forelimb area (CFA), a region that is part of the cortical sensorimotor system. This area in the frontal cortex shares many properties with the primary motor cortex (M1) of primates; injury to M1 results in long-term impairment in reaching and grasping functions[5]. Traditionally, it has been thought that impairment occurs because M1 provides substantial outputs to the motor apparatus in the spinal cord, and thus directly affects motor output function. But it is also recognized that M1 has important interconnections with the primary somatosensory cortex (S1) located in the parietal lobe (Fig. 1A). For example, long-range corticocortical fibers from S1 provide critical information to M1 about the position of the limb in space. Thus, injury to M1 results in impaired motor performance, at least in part, due to disruption in communication between somatosensory and motor cortex[6].

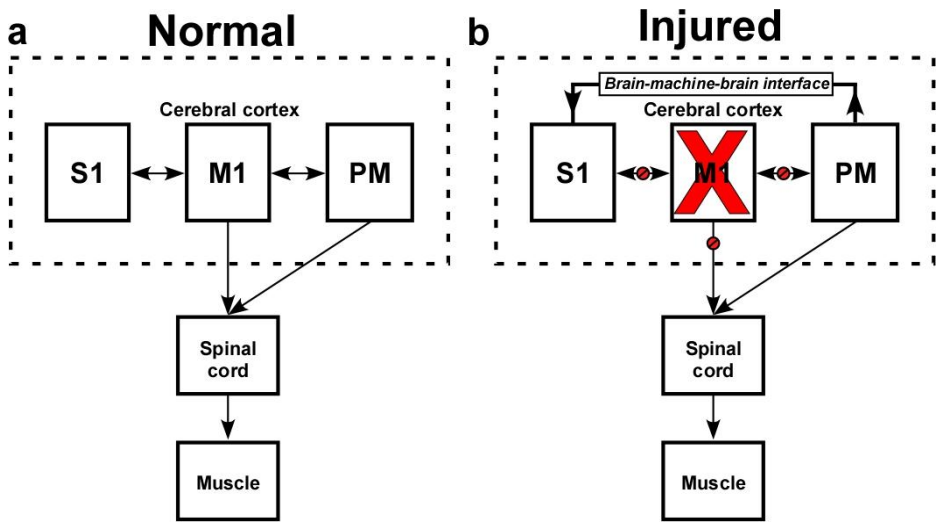

Figure 1. Theoretical model of neuroprosthetic treatment approach after brain injury. (**a**) Normal connectivity of primary motor cortex (M1). (**b**) Hypothetical effect of a brain-machine-brain interface (BMBI) on corticocortical communication. An injury to M1, as might occur in stroke or brain trauma, results in a focal area of necrosis, as well as loss of M1 outputs to the spinal cord. Corticocortical communication between M1 and S1 (and between M1 and PM) is also disrupted, further contributing to functional impairment. Since the uninjured PM also contains corticospinal neurons, it might have the ability to serve in a vicarious role.

To test our hypothesis that functional recovery can be facilitated by creating an artificial communication link between spared somatosensory and motor regions of the brain, we focused on the rat's premotor (PM) cortex. The rostral forelimb area (RFA) is a premotor area in the rodent's frontal cortex that shares many properties with premotor cortex of primates, and is thought to participate in recovery of function after injury to M1[5,7-9]. PM areas are so-named, because the principal target of their output fibers is M1[10]. PM areas also have long-range corticocortical connections with somatosensory areas, but at least in intact animals, they appear to be relatively weak compared with M1's connections with somatosensory cortex[8,11,12].

Our approach was to functionally link the neural activity of the PM forelimb area with activation of the S1 forelimb area following a controlled cortical impact (CCI) to M1 (Fig. 1B). To this end, a microdevice was developed with the ability to record and digitize extracellular neural activity from an implanted microelectrode, discriminate individual action potentials (spikes), then deliver small amounts of electrical current to another microelectrode implanted in a distant population of neurons[13,14] *(*Supplementary Figure 1*)*. This closed-loop system was similar, in principle, to the "Neurochip", used previously by other investigators to demonstrate the effects of local activity-dependent stimulation in intact animals[15]. By linking the activity of one area of the cortex with that of a distant one, a closed-loop brain-machine-brain interface (BMBI) for artificial corticocortical communication was created. Further rationale for the selection of the sites for recording and stimulation, as well as stimulation parameters, are provided in the online version of the paper.

Rats were assigned to three groups: activity-dependent stimulation (ADS) group, open-loop stimulation (OLS) group, and control group. Rats in all three groups received a CCI over the M1 forelimb area. In the ADS

group, rats received electrical stimulation in the S1 forelimb area contingent upon discriminated action potentials in the forelimb area of PM (Fig. 2a). That is, time-amplitude window discriminators determined when action potentials were recorded from a microelectrode implanted in PM. Discrimination of an action potential was followed by delivery of a brief pulse of electrical current (60 µA, 192 µs) to a microelectrode implanted in S1. The wireless, battery-powered microdevice, mounted to the freely moving rat's skull, operated 24 hours per day (Fig. 2b, c). In the OLS group, rats received the same level of electrical stimulation in the S1 forelimb area, but the stimulation was not contingent upon the discriminated action potentials in PM. Instead, the stimulation was delivered arbitrarily at a frequency approximately the same as that in the ADS group and with the timing of stimulation uncorrelated with the discriminated action potentials. In the control group, the microdevice was not implanted and no stimulation was given.

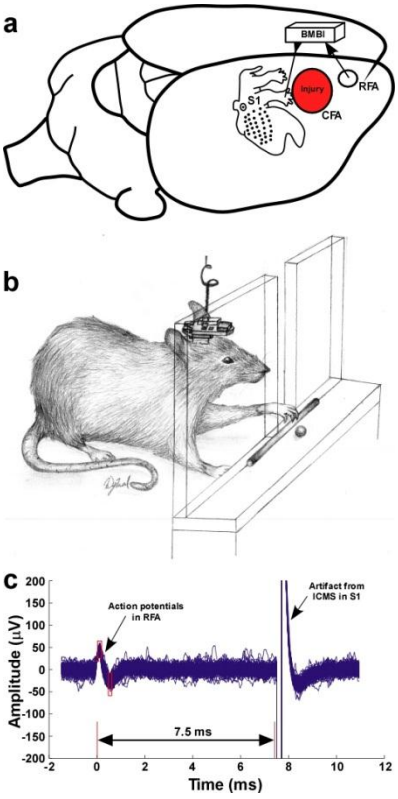

Figure 2. Activity-dependent stimulation protocol. (**a**) Target areas in rat cerebral cortex. A controlled cortical impact (CCI) simulated a focal TBI in the caudal forelimb area (CFA). A recording microelectrode was placed in the rostral forelimb area (RFA), while a stimulating microelectrode was placed in the distal forelimb field of the somatosensory cortex (S1). A BMBI discriminated action potentials in RFA, and after a brief delay, delivered a low-level electrical current pulse to S1. (**b**) Sketch of rat retrieving a food pellet with a BMBI attached to the skull. (**c**) Sample traces of recordings from RFA showing action potentials and stimulus artifacts from intracortical microstimulation (ICMS) current delivered to S1. A total of 100 superimposed traces are shown.

In all rats, the target areas were defined using stereotaxic coordinates and traditional neurophysiological methods. Then, all rats received a CCI confined to the M1 forelimb area, using techniques similar to those used in a prior publication[5]. In the same procedure, in the ADS and OLS groups, chronic microelectrodes were inserted into PM and S1, and connected to the microdevice. The microdevice was then firmly affixed to the skull and activated by insertion of a battery.

Testing motor skill after brain injury

The primary behavioral assay for determining whether ADS resulted in behavioral improvement was a skilled reaching task. This widely used task is a particularly sensitive measure of forelimb motor function after M1 lesions in both rodents and primates. Rats were pre-trained to achieve a minimum criterion score of >70% successful pellet retrievals. After the lesion, rats were tested on the task during assessment sessions on post-lesion Days 3, 5, 8, 14, 21 and 28. During each post-lesion assessment session, rats were tested under two conditions: first with the microdevice stimulation function turned OFF, then with the stimulation function turned ON.

Rats in each of the three groups demonstrated a severe deficit on the skilled reaching task in the first few days after the injury. On post-lesion Days 3 and 5, there were no significant differences in motor performance

among the groups. Rats in the control group (with lesion, but no microdevice) continued to demonstrate a profound deficit that plateaued at only about 25% successful retrievals. In striking contrast, by post-lesion Day 8, rats in the ADS group showed a substantial and statistically significant behavioral improvement in reaching success compared to the other groups in the ON condition ($p = 0.0044$; Fig. 3; Supplementary Movies 1-2). By post-lesion Day 14, the performance of the rats in the ADS group was approximately at pre-lesion levels, and significantly higher than the other groups ($p = 0.0004$). This difference with the other groups remained significant on post-lesion Day 21 ($p = 0.0007$). Substantial improvements in performance in the ADS group were observed regardless of the condition, i.e., whether the microdevice stimulation function was turned ON or OFF during the assessment (Supplementary Figure 2). Rats in the OLS group performed at a level of performance intermediate between the control and ADS groups.

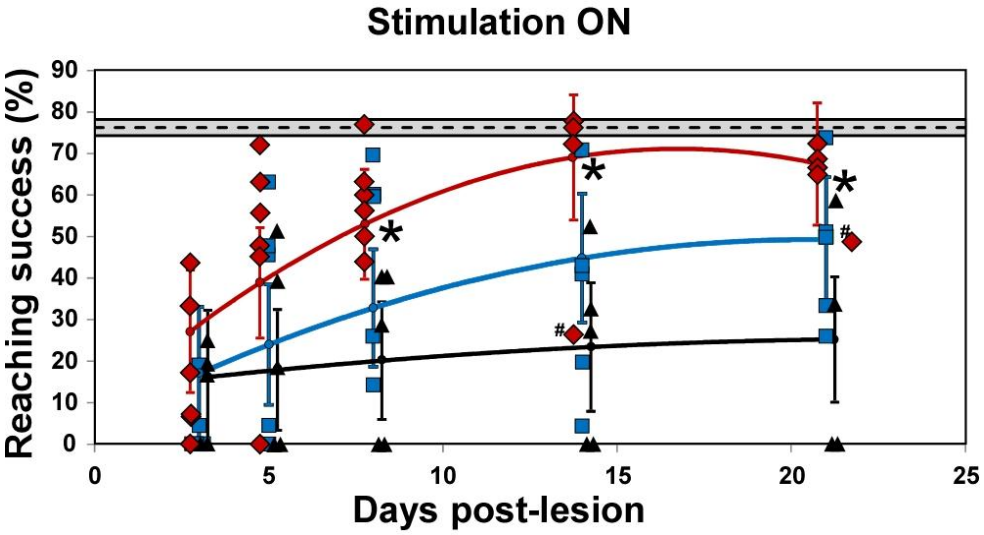

Figure 3. Performance of rats on a skilled reaching task after injury to M1 (ON condition). Activity-dependent stimulation (ADS) group is shown in red, open-loop stimulation (OLS) group is shown in blue and control group is shown in black. Dotted line indicates average pre-lesion performance of all animals in the study. Bounded area indicates the 95% confidence interval. Regression lines are based on a linear mixed model[30]. Error bars represent 95% confidence intervals. *$p < 0.05$ (difference between ADS groupand both OLS and control groups). Because the statistical analysis was an intent-to-treat model, rats were included in the analysis, even if the microdevice was no longer functional. Only one rat in the ADS group had a microdevice that was functional by post-lesion Day 28; thus figures are presented through post-lesion Day 21 (see online version for further details). One rat in the ADS group was tested on post-lesion Day 22, and thus, the data point is offset. Diamonds, squares and triangles represent individual animal data points. # indicates microdevice was not functional (Supplementary Table 1)

Immediate effects within single sessions

Rats in the ADS group often showed substantially improved performance within a single day's session when the microdevice was switched from the OFF to the ON condition. One particularly salient example can be seen in a video of a rat in the ADS group on post-lesion Day 8 (Supplementary Movie 2). In the OFF condition, this rat made many attempts to reach through the opening in the Plexiglas, but was rarely able to do so accurately. Large trajectory errors were made, and relatively few retrievals were completed successfully. Following completion of trials in the OFF condition, the microdevice was programmed to the ON state, a process that required 2-3 minutes. As soon as the microdevice was turned ON, the rat began to retrieve pellets with noticeably enhanced success. Movements tended to be slower, seemingly more deliberate, and fewer errors were made. A statistical analysis of the ADS group between the OFF and ON conditions revealed significantly better performance in the ON condition on post-lesion Days 3 ($p = 0.0003$), 5 ($p = 0.0005$), 8 ($p = 0.0019$) and marginally ($p = 0.0666$) better performance on post-lesion Day 14. The same analysis for the OLS group revealed significantly worse performance in the ON condition on post-lesion Day 3 ($p = 0.0471$), and marginally worse performance on post-lesion Days 5 ($p = 0.0554$) and 8 ($p = 0.0781$) (Fig. 4). This effect tended to dissipate over time, so that no differences were detected between OFF and ON conditions in either group by post-lesion Day 21.

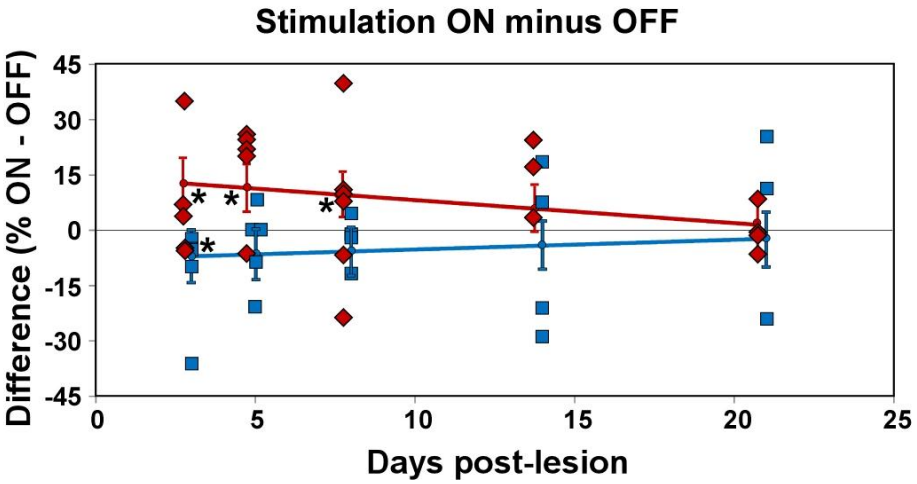

Figure 4. Comparison of motor performance on the skilled reaching task in OFF versus ON conditions. Activity-dependent stimulation (ADS) group is shown in red and open-loop stimulation (OLS) group is shown in blue. Error bars represent 95% confidence intervals. Only rats that were tested in both ON and OFF conditions are included. If the microdevice was not functional, those rats were excluded for that particular day. *$p < 0.05$ (within-group ON/OFF comparisons). Diamonds and squares represent individual animal data points.

This proof-of-concept study indicates that a closed-loop neuroprosthetic microdevice can be employed to generate rapid improvement in motor function after cortical injury, at least in rats with M1 damage. In studies in intact animals, a closed-loop device with similar functionality was shown to induce neurophysiological changes in the function of neurons when applied over a short distance within M1[15]. The present study demonstrates that the extension of the ADS approach to injured brains has demonstrable effects on recovery, greater than those seen with uncorrelated stimulation. The current implementation of the system architecture, employing a lightweight, battery-powered, wireless, miniaturized microdevice for spike-triggered intracortical microstimulation (ICMS), represents a preliminary step in the process of developing implantable BMBIs for neural repair in clinical populations.

Closing the loop in neuroprosthetics

A closed-loop neuroprosthetic microdevice applying ADS across distant cortical areas is a vastly different approach to brain repair than has been achieved to date. Open-loop modulation of the cerebral cortex has been employed in investigational studies and clinical trials for many years. This type of intervention is thought to aid in recovery by reducing the activation threshold of the tissue being stimulated, or by inducing post-tetanic potentiation. For example, an invasive technology using epidural stimulation to provide low-level current pulses over uninjured cortical areas during the execution of rehabilitative training resulted in behavioral improvement associated with dendritic growth and neurophysiological plasticity in rodent and non-human primate models of cortical ischemic injury[16,17]. While initial results in clinical stroke populations were promising, the therapeutic effect of open-loop epidural stimulation was not demonstrated in a randomized clinical trial[18,19]. Nevertheless, noninvasive cortical stimulation approaches (transcranial magnetic stimulation, transcranial direct-current stimulation) continue to attract substantial interest as potential therapies, since they have demonstrated promising results in small groups of stroke survivors[20].

Neuroprosthetic approaches employing closed-loop stimulation in the brain are still uncommon. One neurological indication that may be appropriate for closed-loop stimulation is epilepsy[21]. Since direct or indirect stimulation of a seizure focus can be efficacious in treating intractable epilepsy, various algorithms have been developed to detect epileptiform activity in electroencephalographic (EEG) data, and provide stimulation contingent upon the appropriate EEG signature. The present closed-loop approach differs markedly from the one currently being investigated for epilepsy in that both the recording and stimulating electrodes are penetrating microelectrodes capable of discriminating individual action potentials from extracellular recordings, and microstimulating a relatively small volume of tissue. Whether efficacy can be achieved via less invasive approaches based on ECoG/EEG recordings employing either intracranial electrocorticography or extracranial

electrodes is unknown. However, the precise timing afforded by penetrating microelectrodes may be essential for the type of activity-dependent mechanisms used by the brain to construct long-range communication networks.

Underlying mechanisms

The mechanisms underlying the therapeutic effects of ADS after injury in the present model of TBI are still somewhat speculative. In the 1940s, Donald Hebb postulated that "When one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs … in contact with the soma of the second cell"[22]. This hypothesis has morphed into the modern maxim "Cells that fire together, wire together", a phrase made popular by neuroscientist, Carla Shatz[23]. A large literature has grown from these initial hypotheses, and a neurophysiological phenomenon widely known as "Hebbian plasticity" has formed the basis for many neuroscientific models of learning and memory. Previous studies in intact primates and rodents using ADS or paired-pulse stimulation show the ability for such co-activation to alter output properties of cortical neurons[15,24]. Presumably, the stimulation causes Hebbian-like plasticity to alter existing connectivity within a cortical area.

While functional changes in existing cortical networks can be induced by ADS, related studies also suggest the possibility that ADS alters anatomical connections. First, substantial local axonal sprouting occurs spontaneously in the adjacent intact tissue after a focal cortical insult[25]. This sprouting is limited to 1-2 mm, and is thought to be guided by temporally programmed waves of growth-promoting and growth-inhibiting proteins[26]. Second, studies in our laboratory have demonstrated that long-range axonal sprouting between frontal and parietal cortex occurs spontaneously after focal cortical injury to M1 in non-human primates. An uninjured premotor area in the frontal lobe was found to send axons to part of the S1 hand area within the parietal lobe, a completely novel cortical target[11]. More specific to the present model, after injury to the rat's M1, neurons in PM that normally send corticocortical fibers to M1 show significantly increased expression of genes involved in neurite growth and guidance[27]. Third, low-frequency synchronous oscillatory activity appears to be necessary for novel post-injury sprouting to occur[28]. Thus, during the initial weeks post-injury, when axonal sprouting is thought to be most robust, ADS may temporally couple the activity of remote cortical locations that are not normally co-activated or interconnected. This artificial temporal pairing may encourage growing axons to migrate toward and terminate in the coupled region. Thus, two interdependent mechanisms may explain the effects of ADS on post-injury behavior: 1) it helps drive Hebbian-like plasticity in pre-existing fibers; 2) it promotes spontaneously sprouting axons to terminate in areas with high temporal correlation. While anatomical changes cannot be ruled out, the rapid behavioral gains observed in this study suggest that physiological changes in synaptic efficacy, either between cortical areas, between cortical and subcortical structures, or both, underlie the recovery.

Implications for neurological treatment

Linking spared cortical motor and sensory areas through ADS is an effective treatment for M1 damage in a rodent model of brain injury. This treatment may be effective for many other types of injuries resulting from stroke and TBI, as well as a variety of neurological syndromes that are thought to be related to disruption of cortical communication. In the 1960s, Norman Geschwind identified several disorders collectively called "disconnection syndromes", revolutionizing the field of behavioral neurology[29]. The consideration of closed-loop approaches to repair of cortical disconnection syndromes may open up treatment options for a variety of conditions in which neural communication is disrupted, whether due to disease, injury or idiopathic causes.

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